Remdesivir

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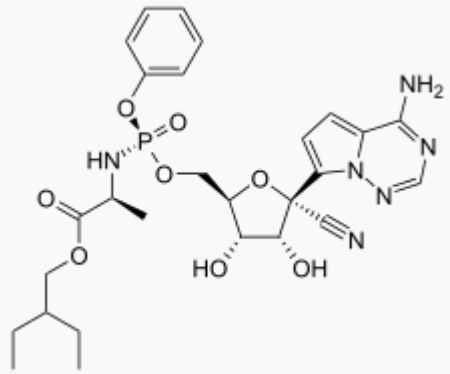
Remdesivir	
	
Clinical data	
Other names	GS-5734
Routes of administration	Intravenous
ATC code	None
Legal status	
Legal status	Investigational
Identifiers	
IUPAC name[show]	
CAS Number	1809249-37-3✓
PubChem CID	121304016
DrugBank	DB14761✓
ChemSpider	58827832
UNII	EW5GL2X7E0
KEGG	D11472
ChEBI	CHEBI:145994
ChEMBL	ChEMBL4065616
Chemical and physical data	

Formula	$C_{27}H_{35}N_6O_8P$
Molar mass	602.585 g·mol^{-1}
3D model (JSmol)	Interactive image
SMILES[show]	
InChI[show]	

Remdesivir is an antiviral medication developed by the American biopharmaceutical company Gilead Sciences. It is a nucleotide analog, specifically an adenosine analogue, which inserts into viral RNA chains, causing their premature termination. It was studied during 2020 as a possible post-infection treatment for COVID-19.[1]

Contents

Research

Remdesivir was created and developed by Gilead Sciences, under the direction of scientist Tomáš Cihlář,[2] as a treatment for Ebola virus disease and Marburg virus infections.[3] Gilead Sciences subsequently discovered that remdesivir had antiviral activity *in vitro* against multiple filo-, pneumo-, paramyxo-, and corona-viruses.[4]

COVID-19

See also: Coronavirus disease 2019 § Research, and COVID-19 drug repurposing research

As of April 2020, remdesivir was viewed as the most promising treatment for COVID-19 by Johns Hopkins University.[5] Data from one randomized controlled trial was released early in error and before peer review; it did not show improvement. Gilead Sciences stated that due to low enrollment the study was halted while a non-

associated researcher stated it does mean if there is any benefit, then that benefit will be small.[6] Other clinical trials were underway or planned.[7][8][9][10][11][12][13][14][15][16][17]

On 18 March 2020, the World Health Organization (WHO) announced the launch of a trial that would include one group treated with remdesivir.[18][19] While a cohort study published in April 2020, saw possible improvement, determining whether or not the medication is effective will require a randomized controlled trial.[20]

In January 2020, Gilead began laboratory testing of remdesivir against SARS-CoV-2, stating that remdesivir had been shown to be active against severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) in animal models.[21][22][23] In March 2020, a small trial of remdesivir in rhesus macaque monkeys with COVID-19 infections found that it prevents disease progression.[24][25] On 21 January 2020, the Wuhan Institute of Virology applied for a Chinese "use patent", for treating COVID-19.[26]

Ebola

On 9 October 2015, the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) announced preclinical results that remdesivir had blocked the Ebola virus in Rhesus monkeys. Travis Warren, who has been a USAMRIID principal investigator since 2007, said that the "work is a result of the continuing collaboration between USAMRIID and Gilead Sciences".[27] The "initial screening" of the "Gilead Sciences compound library to find molecules with promising antiviral activity" was performed by scientists at the Centers for Disease Control and Prevention (CDC).[27] As a result of this work, it was recommended that remdesivir "should be further developed as a potential treatment."[27][3]

Remdesivir was rapidly pushed through clinical trials due to the West African Ebola virus epidemic of 2013–2016, eventually being used in people with the disease. Preliminary results were promising; it was used in the emergency setting during the Kivu Ebola epidemic that started in 2018, along with further clinical trials, until August 2019, when Congolese health officials announced that it was significantly less effective than monoclonal antibody treatments such as mAb114 and REGN-EB3. The trials, however, established its safety profile.[28][29][30][3][31][32][33][34]

Access

On 17 March 2020, the drug was provisionally approved for use for COVID-19 patients in a serious condition as a result of the outbreak in the Czech Republic.[35] On 20 March 2020, United States President Donald Trump announced that remdesivir was available for "compassionate use" by people with COVID-19; FDA Commissioner Stephen Hahn confirmed the statement at the same press conference.[36] On 23 March 2020, Gilead voluntarily suspended access for compassionate use (excepting cases of critically ill children and pregnant women), for reasons related to supply, citing the need to continue to provide the agent for testing in clinical trials.[37][38]

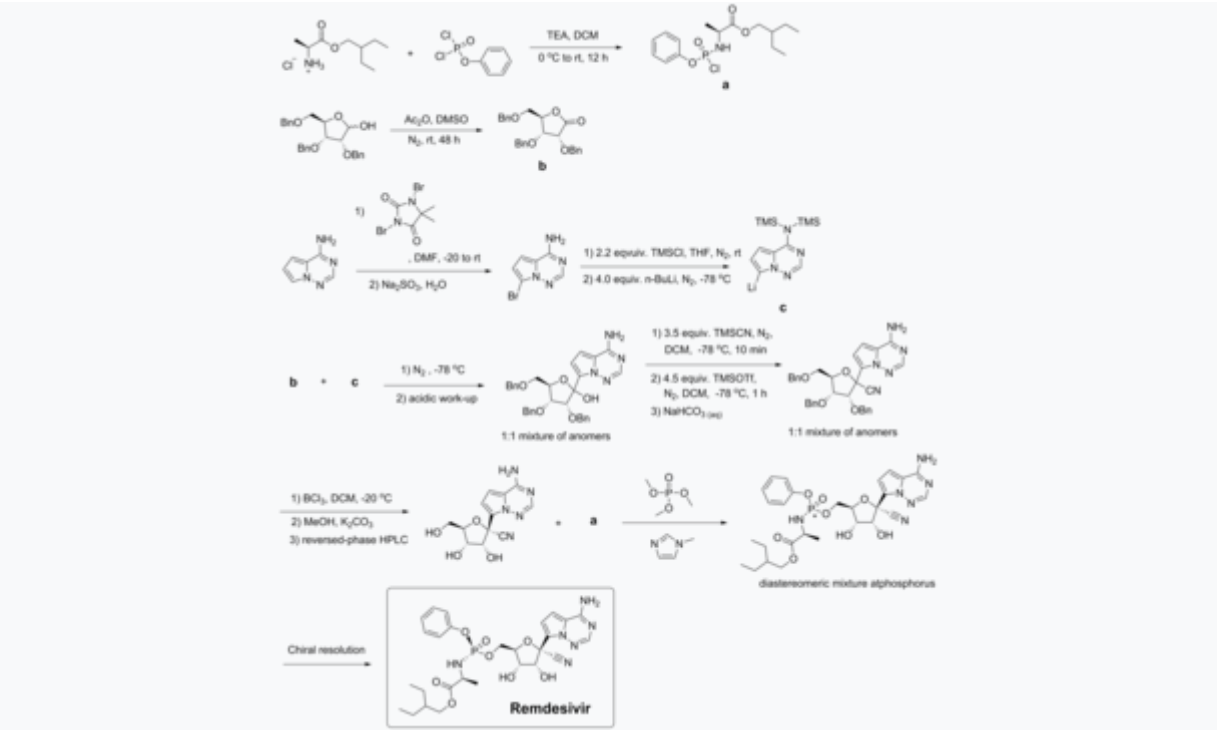
As of 11 April 2020, access in Canada was only to those who will be involved in a clinical trial.[39]

Mechanism of action and resistance

Remdesivir is a prodrug that metabolizes into its active form GS-441524. An adenosine nucleotide analog, GS-441524 interferes with the action of viral RNA-dependent RNA polymerase and evades proofreading by viral exoribonuclease (ExoN), causing a decrease in viral RNA production.[40] Though in some viruses, such as the respiratory syncytial virus but not Ebola virus, it causes the RNA-dependent RNA polymerases to pause, its predominant effect is to induce an irreversible chain termination. Unlike with many other chain terminators, this was not mediated by preventing addition of the immediately subsequent nucleotide, but is instead delayed, occurring after five additional bases have been added to growing RNA chain.[41]

Mutations in the mouse hepatitis virus RNA replicase that cause partial resistance to remdesivir were identified in 2018. These mutations make the viruses less effective in nature, and the researchers believe they will likely not persist where the drug is not being used.[40]

Synthesis



Synthesis of remdesivir in structural formulae

Remdesivir can be synthesized in multiple steps from ribose derivatives. The figure to the right is one of the synthesis routes of remdesivir invented by Chun and coauthors from Gilead Sciences.[42] In this method, intermediate **a** is firstly prepared from L-alanine and phenyl phosphorodichloridate in presence of triethylamine and dichloromethane; triple benzyl-protected ribose is oxidized by dimethyl sulfoxide with acetic anhydride and give the lactone intermediate **b**; pyrrolo[2,1-f] [1,2,4]triazin-4-amine is brominated, and the amine group is protected by excess trimethylsilyl chloride. n-Butyllithium undergoes a halogen-lithium exchange reaction with the bromide at −78 °C (−108 °F) to yield the intermediate **c**. The intermediate **b** is then added to a solution containing intermediate **c** dropwise. After quenching the reaction in a weakly acidic aqueous solution, a mixture of 1:1 anomers was obtained. It was then reacted with an excess of trimethylsilyl cyanide in dichloromethane at −78 °C (−108 °F) for 10 minutes. Trimethylsilyl triflate was added and reacts for one additional hour, and the mixture was quenched in an aqueous sodium hydrogen carbonate. A nitrile intermediate was obtained. The protective group, benzyl, was then removed with boron trichloride in dichloromethane at −20 °C (−4 °F). The excess of boron trichloride was quenched in a mixture of potassium carbonate and methanol. A benzyl-free intermediate was obtained. The isomers were then separated via reversed-phase HPLC. The optically pure compound and intermediate **a** are reacted with trimethyl phosphate and

methylimidazole to obtain a diastereomer mixture of remdesivir. In the end, optically pure remdesivir can be obtained through chiral resolution methods.

Terminology

Remdesivir is the international nonproprietary name (INN)[43] while the development code name was GS-5734.[44]

Other animals

Remdesivir was shown in 2019 to have possible promise for treating feline infectious peritonitis caused by a coronavirus.[45] It has not been evaluated or approved by the Food and Drug Administration (FDA) for the treatment of feline coronavirus or feline infectious peritonitis but has been available since 2019 through websites and social media as an unregulated black market substance as confirmed by the UC Davis School of Veterinary Medicine.[46]

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External links

- *"Remdesivir". Drug Information Portal. U.S. National Library of Medicine.*

hide

RNA virus antivirals (primarily J05, also S01AD and D06BB)

NS3/4A protease inhibitors (–previr)	Asunaprevir Boceprevir‡ Ciluprevir§ Danoprevir† Faldaprevir‡ Glecaprevir Grazoprevir Narlaprevir Paritaprevir Simeprevir Sovaprevir† Telaprevir‡ Vaniprevir Vedroprevir§ Voxilaprevir
NS5A inhibitors (–asvir)	Daclatasvir# Elbasvir Ledipasvir Odalasvir† Ombitasvir Pibrentasvir

	Ravidasvir[†] Ruzasvir[†] Samatasvir[†] Velpatasvir
NS5B RNA polymerase inhibitors (–buvir)	Beclabuvir[†] Dasabuvir[#] Deleobuvir[§] Filibuvir[§] GS-6620[§] IDX-184[§] Setrobuvir[§] Sofosbuvir[#] Radalbuvir[†] Uprifosbuvir[†]
Combination drugs	Elbasvir/grazoprevir Glecaprevir/pibrentasvir Ledipasvir/sofosbuvir[#] Ombitasvir/paritaprevir/ritonavir[#] Sofosbuvir/daclatasvir Sofosbuvir/velpatasvir[#] Sofosbuvir/velpatasvir/voxilaprevir

viral entry: Pleconaril[†]

Baloxavir marboxil

Pimodivir[†]

Umifenovir

adamantane derivatives/*M2 inhibitors* (Adapromine

Amantadine

Rimantadine)

neuraminidase inhibitors/*release phase* (Oseltamivir[#]

Zanamivir

Peramivir, Laninamivir[†])

Interferon	Interferon alfa 2b Peginterferon alfa-2a[#] Peginterferon alfa-2b[#]
Multiple/unknown	FICAR[§]

Favipiravir

Galidesivir†

Remdesivir†

MK-608§

NITD008§

Mericitabine†

Merimepodib§

Moroxydine

Presatovir†

Ribavirin#

Taribavirin†

Triazavirin

Valopicitabine†

- #WHO-EM
- ‡Withdrawn from market
- Clinical trials:
  - †Phase III
  - §Never to phase III

- **Medicine portal**
- **Viruses portal**

Categories:

- Drugs not assigned an ATC code
- Anti-RNA virus drugs
- Antivirals
- Experimental drugs
- Gilead Sciences
- Heterocyclic compounds (2 rings)
- Nitriles
- Nitrogen heterocycles
- Nucleotides
- Phenol esters
- Phosphoramidates